RU-486, STATUS REPORT ON THE U.S. COMMERCIALIZATION PROJECT, TRANSFER OF ANTIPROGESTIN TECHNOLOGY TO THE UNITED STATES

Y 4. SM 1: 103-80

RU-486, Status Report on the U.S. C... RING

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY

OF THE

COMMITTEE ON SMALL BUSINESS
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

WASHINGTON, DC, MAY 16, 1994

Printed for the use of the Committee on Small Business

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RU-486, STATUS REPORT ON THE U.S. COMMERCIALIZATION PROJECT, TRANSFER OF ANTI-PROGESTIN TECHNOLOGY TO THE UNITED STATES

MONDAY, MAY 16, 1994

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY,
COMMITTEE ON SMALL BUSINESS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:03 a.m., in room 2359–A, Rayburn House Office Building, Hon. Ron Wyden (chairman of the subcommittee) presiding.

Chairman WYDEN. The subcommittee will come to order. Today the Subcommittee on Regulation and Business Opportunities and Technology will continue its oversight of Government efforts to assist American pharmaceutical companies in the development and commercialization of antiprogestin drugs. This important new line of drugs includes RU-486, the French abortifacient therapy, that also shows promise for treating a variety of conditions and diseases threatening the health of many Americans.

Our focus today is the status of negotiations now proceeding to license RU-486 to the Population Council, a nonprofit foundation. It is my view that this licensing negotiation, now well into its second year, offers the best hope for American women to have a safe, effective alternative to surgical abortion before the end of this century. Delays in concluding this negotiation, therefore, have been very troubling.

Finally, the Population Council and Roussel Uclaf, the French maker of the drug, have come to an agreement to bring this drug to the United States.

This is an extraordinary victory for American women. Our country is turning away from a time when women trying to bring this drug into the United States were the subject of stop and frisk searches by U.S. border guards. Today, medical science is finally defeating political science.

I would like to take the opportunity at this time to pay special credit to the Secretary of Health and Human Services, Donna Shalala, who did so much to make this day possible. Doctor David Kessler, the Commissioner of the Food and Drug Administration, will be testifying later on behalf of the administration. Donna Shalala had to attend a meeting with the President, but in my

opinion, the Secretary deserves great credit for making this day possible.

RU-486 will get a fair and dispassionate analysis now by the Food and Drug Administration. I feel that within 2 years, those tests are going to lead to Government approval to the general distribution of the drug.

For almost 4 years this subcommittee has been following the debate over the introduction of RU-486 into the United States. Along with the detailed investigation of the safety and efficacy of this product in foreign markets, our inquiry has questioned whether the previous Presidential administration actively discouraged the introduction of this product in our country.

The resulting controversy has, for better or worse, transformed this pharmaceutical into a lightening rod in the abortion debate. Although an important new medical agent in its own right, this drug's political symbolism has very nearly over shadowed its pharmacological importance.

Very clearly, RU-486 demonstrates the kinds of political problems dual use drugs like this may face in the future. Here is a pharmaceutical used widely in Europe as an abortifacient, but its chemical properties also seem therapeutic for a variety of diseases and other problems ranging from Cushing's Syndrome to meningioma.

In the United States, major trials are under way to treat breast cancer with RU-486 and also to use the product as a morning after contraceptive. Our country faces a choice. Should we exile an important new product, an agent that could have many strong therapeutic values, based on the fact that one of the drug's uses fails to pass a political litmus test? Alternatively, should our country use good sense and good judgment to manage our health product development activity, including the regulation of new drugs and devices?

I am convinced that this drug's controversial history led to its placement on the import alert list, a decision that led to the now famous search and seizures. The cascading political fallout generally had a debilitating effect on a variety of medical experimentation with RU-486 in our country.

The agreement announced today reverses this unwholesome development. The agreement sends a strong statement to the international, medical and pharmaceutical community at a time that the U.S. Government is committed to see a change in attitude. Witnesses coming before this subcommittee today will offer, first, detailed explanations of the clinical trials leading to the likely approval of this drug; second, the partnerships which will be built between small manufacturers and distributors to bring this drug to market; and third, the probable ways and means of access to this therapy by American women who choose RU-486 over surgical abortion.

We welcome Doctor David Kessler, Commissioner of the Food and Drug Administration, who will explain the regulatory process for this drug over the next 2 years. Primary to this process is the degree to which Dr. Kessler will weigh clinical experience with this drug in Europe where more than 150,000 women have used RU-486 since the late 1980's. Also, the FDA will have the challenging

task of assessing the development of the medical practice system for administration and supervision of RU-486.

Here the differences between the French health care system and our own will have to be rationalized so that RU-486 has the widest possible availability with the strongest possible safety protection. The French system is government-owned and operated. Ours is a mixture of public and private hospitals, religious and secular, profit and nonprofit. Sponsors of this drug will have to develop a consistent medical management system, including standards of practice that will make the delivery of this drug as safe and effective as the drug itself.

Mr. James Boynton, representing the Population Council, will explain the logistics of the clinical trials. Of greatest interest to the subcommittee will be restrictions and requirements for use of the drug. Will RU-486, for example, be limited to hospital use only, or will women have the opportunity to choose this therapy in the privacy of their own doctor's office?

Finally, the subcommittee welcomes Mr. Lester Hyman, representing Roussel Uclaf. Mr. Hyman and Mr. Boynton have labored long and hard to conclude this important licensing agreement and they have our congratulations. We are also especially pleased that Congresswoman Patricia Schroeder, the Co-Chair of the Congressional Women's Caucus, a bipartisan group on Capitol Hill, is with us this morning.

[Chairman Wyden's statement may be found in the appendix.]

It is the practice, Congresswoman Schroeder, to swear all the witnesses who come before our subcommittee. Do you have any objection to being sworn as a witness?

Mrs. SCHROEDER. Not at all.

Chairman WYDEN. Please rise and raise your right hand.

[Witness sworn.]

Chairman WYDEN. Welcome, Congresswoman Schroeder. We know that you have been mobilizing support for these kinds of women's health issues for many, many years and have done much to make this day possible. We will make any prepared remarks you would like a part of the record. Please proceed as you wish.

TESTIMONY OF HON. PATRICIA SCHROEDER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Mrs. SCHROEDER. Thank you so much, Congressman Wyden. I am basically here to put a historical context on it. I guess it is because I have all this gray hair. As dean of the women and as Chair of the Caucus, Co-Chair of the Caucus of which, of course, you are a member, I think this is truly a historic day and a historic week. I really can't believe that it is happening, it is finally happening.

Americans always felt that it was part of their birthright to have medically available whatever was the state of the art, and what was out there. We did not belong to the flat Earth caucus. We were people who believed that science could solve a lot of things. We have always been very, very, proud of our medical science.

As you know, in the 1980's, that got amended a bit, especially as it came toward women. Very tragically, women got what was politically correct according to the far right. We saw many of our own drug companies stop research in reproductive choices. I think we

were down to only one company doing some research by the end of that decade, and we had started out with 12 or 13, mainly because it was just so unpopular and so everybody backed off, because they were so afraid of what the repercussion might be. We know that violence was tolerated at clinics where reproductive services were being delivered to women.

Of course, women also got 85 percent of the—85 percent of the women got all their health care at those clinics. That made no difference. They winked at the violence, and, of course, this is a—we just saw the historic passing by both bodies of the face bill that will end that violence. So, you had the feeling that they were terribly frightened of RU-486 because you might not have to go and be in a clinic to get it as you did with a surgical procedure, and therefore it would be difficult to figure out where to organize and do all that.

Well, now you have got a two-fer. You have got the face bill with the Federal Government moving toward and you have got RU-486 coming in. I just think that that is amazing and so women now can become full-fledged citizens.

The other thing that you said that I think is so terribly important that really showed how crazy this kind of censorship is, medical censorship by any government, is that it has fallout in all sorts of other areas. You sat with me and we worked very hard with the man named David Grow who was a banker from Atlanta who had been a big supporter, I think, of the other party, and was absolutely horrified to find out that after several brain surgeries for tumors, he was told he could not have RU-486 brought in to treat him, even if it was just turned over to the university and just looked at, and just handled there, because they were so afraid it might leak out and get an abortion.

Now, that made him and his family very angry and you were kind enough to give a hearing for that. I would like to ask unanimous consent to put in the record a letter from his family saying that now here we are 2 years later, his MRI shows no evidence left of tumors, and it would have never happened if you hadn't had a hearing and we hadn't embarrassed the administration into giving this one man a compassion exemption. The tragedy was you couldn't have a hearing for every single person that needed that compassion exemption, and a lot of people didn't know that some of these antiprogestin drugs such as RU-486 and others that were being withheld did have some potential to treat the different ailments they have.

Well, that kind of censorship and that kind of nonsense is over. So, I think it is very fitting to just frame this in a historical setting because it truly is and I think American women are being treated now as men are. They are now going to be able to have what is medically necessary and appropriate, and senators don't get to select for them and congressmen don't select for them, an administration doesn't select for them, and let us hope we reclaim that, rather than the extreme right having a political correct veto from their own narrow vantage. So, thank you, thank you for letting me come by and thank you for your continuing hard work and the Secretary's and everyone else who made this day possible.

[The information may be found in the appendix.]

Chairman WYDEN. Well, thank you for an excellent statement. I thought maybe just for a minute you might describe what this situation was like in the 1980's, as opposed to dealing now with Secretary Shalala and the President. It seems to me we saw a real sea change when they came to office. Secretary Shalala has essentially bird-dogged this every step of the way in an effort to try to make this agreement come together. I thought maybe you might contrast that to what we saw in the 1980's.

Mrs. SCHROEDER. Well, again, I guess I can go back to the gray hair, because my generation has lived through this even pre1980's. I went to Harvard Law School, and was married at the time, and at that time it was a State that didn't allow birth control pills. Before Griswald versus Connecticut, if you had bought your birth control pills and brought them into Massachusetts and had ever gotten caught, you could be accused of a crime. That was just the 1960's. So, I feel very strongly about this because being a law student, understanding the law, but deciding I didn't think it was fair that just because the State where my law school happened to be and of which I was not a resident had this restriction, I could have been made a criminal. So, I felt very strongly about that.

So when we got into the 1980's and we found women wanting a lot of these things, and we even had trouble getting NORPLANT in. Remember how long it took to get NORPLANT in? The caucus tried over and over again to meet with administration officials. Women's Caucus had always been meeting with administration officials up until the Reagan and Bush administration came in, and they never met with us. They would meet with every other group in the Congress, but they would never meet with the women. They didn't want to talk about these issues, they didn't want to deal with these issues, and we just were totally ignored.

I have a bunch of letters, I think, that will probably fill this room of requests from the Congresswomen, and even the Republican Congresswomen. We are bipartisan, asking to meet on these issues, these very tough issues, from this to family leave to everything else. The answer was always no, no, no.

Now, to see a whole different atmosphere where last week I was fortunate enough to get to have breakfast with Secretary Shalala, she was telling me how this was coming, how hard she is working on it. You kind of think that is what Government is supposed to be doing, trying to open these doors for people and not close them. But it is hard for, I think, people like you and I to adjust to it after we had gone through the very long period where the doors were shut in our face. They really did not return letters or phone calls.

Chairman WYDEN. Well, I have no further questions. For all the years and for all the effort, I think women in our country owe you a great deal of gratitude. I look forward to working closely with you. We still have the Anti-Progestin Testing Act, introduced in this Congress, to go forward with other kinds of dual-purpose drugs. Unless you have anything further, we will excuse you at this time.

Mrs. SCHROEDER. I don't, but I thank you and I think many people in this room, it is a very historic and wonderful day. Thank you.

Chairman WYDEN. Thank you. Our next witnesses will be Dr. David Kessler and Ms. Mary Pendergast, representing the Food and Drug Administration. Dr. Kessler, if you and Ms. Pendergast will come forward. We welcome you to our subcommittee again, where you have been on a number of occasions and served well.

It is the practice, as you know, to swear in all our witnesses. Do either of you have any objection to being sworn? Please raise your right hand.

[Witnesses sworn.]

Chairman WYDEN. We will make your prepared statement a part of the hearing record in its entirety. Dr. Kessler, would you like to begin with a prepared statement?

TESTIMONY OF HON. DAVID KESSLER, M.D., COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC, ACCOMPANIED BY MARY PENDERGAST, DEPUTY COMMISSIONER SENIOR ADVISER TO THE COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION

Dr. KESSLER. Thank you very much, Mr. Chairman. I am joined by my colleague, Ms. Mary Pendergast, who is Deputy Commissioner Senior Adviser to the Commissioner at the Food and Drug Administration.

Mr. Chairman, the Food and Drug Administration has encouraged the submission of a new drug application for RU-486 for interruption of early pregnancy so that we can determine whether it is safe and effective for that indication. If there is a safe and effective medical alternative to any surgical procedure, American women should have access to that drug regimen.

We cannot form, however, any definitive conclusions about the drug's safety and effectiveness or approve it for marketing in the United States without first reviewing the studies and other data that would be submitted in a new drug application.

On January 22, 1993, President Clinton issued a memorandum to the Secretary of Health and Human Services directing her to assess initiatives to promote the testing and licensing in the United States of RU-486. In response, FDA's efforts have been focused on encouraging and facilitating the submission of a new drug application.

Immediately after the President issued the memorandum, I wrote to Dr. Edward Sakiz, president of Roussel Uclaf, and requested a meeting to discuss the possible therapeutic uses of antiprogestational drugs, and in particular FDA's interest in receiving a new drug application for RU-486 for interruption of early pregnancy.

Both Secretary Shalala and I also let Heochst AG, Roussel Uclaf's parent corporation, know of our interest. On February 24, 1993, senior representatives of FDA and Roussel Uclaf met to discuss the clinical and manufacturing data that FDA would need to review as part of a new drug application for an abortifacient indication.

At that meeting, FDA received a strong commitment from Dr. Sakiz that he would find a way to bring RU-486 to the U.S. market. Doctor Sakiz stated that Roussel Uclaf would not be directly involved, but instead would work through a third party in **the**

United States. Dr. Sakiz also committed to making the drug available for research on other potential uses.

FDA and Roussel Uclaf agreed to continue to work on this matter until remaining issues could be resolved. At an April 20, 1993 meeting at FDA, Roussel Uclaf indicated its willingness to modify its 1982 contract with the Population Council, a nonprofit scientific and technical organization. These modifications would permit the Population Council and its sub licensees to produce, test, and distribute RU-486 in the United States.

The Population Council agreed to work to identify a manufacturer for RU-486 for the U.S. market and to begin clinical trials to test the drug in the United States. At that point, we thought the clinical trials on RU-486 would begin soon in the United States. This proved not to be the case.

Before the Population Council would begin clinical trials, the Population Council and Roussel Uclaf undertook complex negotiations pertaining to the transfer of the RU-486 patents and the way the drug would be distributed in the United States. After a year of these negotiations, on April 14, 1994, Secretary Shalala and senior department officials, including Ms. Pendergast and myself, met with the heads of Roussel Uclaf and the Population Council.

At that meeting, the parties indicated their willingness to continue their negotiations, and the Secretary made it clear to the negotiating parties that agreement on all outstanding issues should be reached no later than May 15, 1994.

We are pleased that Roussel Uclaf and the Population Council have concluded their negotiations, and that Roussel Uclaf has donated the patents on RU-486 without remuneration. We anticipate that the Population Council will now pursue the clinical testing of RU-486 in the United States. We, the Food and Drug Administration, will work with the Population Council to make certain that their clinical trials are well-designed and carefully conducted, in order to provide useful information on how the drug might be properly used in this country. FDA will review the application carefully under appropriate medical and scientific criteria.

It should be recognized that the termination of a pregnancy is not a simple procedure. Whether it is done surgically or through a medical regimen. Women should not think that pregnancy termination using a medical regimen will be simple. It will not be.

In Europe where RU-486 has been used in over 150,000 women, the procedure requires several visits to a medical facility, a precise dosing scheme using two different drugs, and close monitoring to care for women who may experience excessive bleeding and other complications. We anticipate that any use of RU-486 in the United States would have to follow strict distribution and use controls.

Ms. Pendergast, the Deputy Commissioner, and I, are prepared to answer your questions.

[Dr. Kessler's statement may be found in the appendix.]

Chairman WYDEN. Doctor, thank you very much. Thank you also, for all of your efforts to ensure that this drug be handled in a fashion consistent with your regulatory responsibilities. That is what I really want to address. Your job, the agency's job, is to determine the safety and effectiveness of the drug.

As you stated, the Population Council will have to file a new drug application to determine the steps in your decisionmaking process. Short of that however, could you forecast what determinants the FDA will use in assessing RU-486 as an abortifacient?

Ms. PENDERGAST. We are planning on treating this like any other drug, which is to say that we intend to apply the same rigorous medical and scientific standards in our review of this drug, as any other. We will work with the company to design good clinical trials for the testing of this drug in this country. We will review, then, the new drug application if one is submitted, and audit the data submitted in that new drug application to make sure that the medical and scientific evidence that we have is as accurate as possible.

Finally, the FDA intends to work closely with the sponsor of this drug to make certain that there is a distribution and use scheme for this drug that would permit it to be used safely in this country.

Dr. KESSLER. Mr. Chairman, we have several IND's that are in effect for the study of this drug. We have already looked at chemistry and pharmacology data on this drug. We have also reviewed published studies on the clinical effectiveness that are in the medical literature.

Obviously, an important part of our review would be to audit the studies that are published in the medical literature.

Chairman WYDEN. Now, Dr. Kessler, in the past the Agency said that it wants to look closely at the European clinical experience with this drug. Could you briefly describe what you consider the highlights of the European experience? In effect, we would be interested in the points that most interest you as an FDA regulator.

Dr. KESSLER. It is probably accurate to say, Mr. Chairman, that there have been about 20 significant studies on the use of this drug, and certainly there are many other studies that have been conducted, some with smaller numbers of patients. I would estimate that there have been between 20,000 and 30,000 patients that have been enrolled in clinical trials, and as you mentioned earlier, there are over 150,000 patients that have received the drug after it has been approved in other countries.

To answer your question, and to give you a sense of what we look at, let me refer to one particular study and perhaps go through that. It is a May 27, 1993 study, that was published in the New England Journal of Medicine. Again, our obligation is to review data like that and to audit that data.

The paper is senior authored by Peyron. There are two series in that paper, two series and two studies that are reviewed and documented. Let me just take you through the first series in study one, which involved 488 women. The mean duration of amenorrhea was 45 days, 45 days from the last period. Some women had to be excluded from the study. One had an ectopic pregnancy, that would not be appropriate. One had longer amenorrhea, for more than 49 days. There were several that were excluded for a lack of appropriate follow-up.

The rate of effectiveness, and define that as termination of pregnancy and complete expulsion, in that series of 488 patients, was 96.9 percent. Termination of pregnancy occurred in 2.9 percent of women within 48 hours, 60 percent within 4 hours of the second

drug being administered, the prostaglandin, and 33.2 percent thereafter.

The failures included ongoing pregnancy in 0.8 percent, incomplete abortions in 1.8 percent, and surgical procedures being required for heavy bleeding in 0.4 percent. All the women had uterine bleeding. The mean duration was 9 days. One woman in that series needed a transfusion. Eighty percent had uterine cramps.

On the scale, on a pain scale with zero being no pain and 100 being the most severe pain that can be perceived, the mean number was 31 on that scale between 0 and 100. The side effects of nausea, vomiting, and diarrhea occurred anywhere between 4.3 and 14 percent of women. Six women had a substantial but a transient decrease in blood pressure. I go through that series just to give you a sense of the kind of issues that we will be looking for in any application.

Chairman WYDEN. I think a lot of people would say that since a great deal of data on the safety and effectiveness of the drug as an abortifacient is already available. What exactly, in your opinion, are the U.S. trials supposed to prove?

Will you look at medical practice issues? I think a lot of people look at this huge volume of data and say, well, what are the U.S. trials supposed to do?

Ms. PENDERGAST. There are medical practice issues that we will be looking at. In the countries where the drug is already approved and used, the health care delivery systems are somewhat different than the health care delivery system here in the United States. For example, in France, a pregnancy termination only takes place in specially designated government-run clinics. We don't have a comparable system here in the United States. So, one of the questions that will be looked at in any clinical trials is how can one use this drug safely and properly in the more diverse health care settings that appear in this country.

Another reason for clinical trials is to help educate the doctors of this country in how to properly use and monitor this drug. So, it gives us good information about what doctors need to know before they can begin administering the drug.

Chairman WYDEN. Do you foresee, for example, the trials looking at some sort of baseline health and safety requirement for practitioners so they would be eligible to dispense and administer the drug?

Ms. PENDERGAST. We will be looking at the kinds of qualifications of physicians. We want to make certain that the physicians are well-qualified to use this drug; that there is access to appropriate backup for any complications that might occur with use of the drug; and that the distribution of the drug be carefully tracked so that it wouldn't be used in other environments where it could not be used safely.

Chairman WYDEN. But we are certainly talking about potential delivery systems that would include a wide variety of settings, both public and private. Is that correct?

Ms. PENDERGAST. We would anticipate that. This is a big country and women live in large cities and in small rural communities, and a major question to be asked and answered is how can you properly

and safely use this drug in the wide variety of health care settings available to women?

Chairman WYDEN. In this inquiry you will unquestionably be looking at the specific prospect of the use of RU-486 in doctors' offices. Isn't that correct?

Ms. PENDERGAST. That is correct.

Dr. KESSLER. Mr. Chairman, the issues that have concern to the Agency is to assure that appropriately trained people be the ones who are responsible for using the drug, that there be backup procedures available, and the drug be tracked so that no inappropriate use of the drug would take place. Those are the concerns. If those concerns can be met, it is likely that any setting that can meet those concerns could, in fact, carry out the procedure.

Chairman WYDEN. Doctor, I know you didn't get into all of the details of the agreement, but I am interested in asking you some questions dealing with some of the issues relating to the public interest involved in this patent gift to the Population Council.

First and foremost, we are interested in knowing if the Government is involved in any way as an indemnifier for any party for any product liability which could occur at any point?

Dr. KESSLER. The Government will not be involved in any way in indemnification of any of the parties.

Chairman WYDEN. Is it fair to say that the Government acts as an interested observer of the process? Other than your job as a regulator, that is essentially the position of the Government?

Dr. KESSLER. That is correct, Mr. Chairman.

Chairman WYDEN. The Government will receive no patent rights as part of this agreement that was reached this weekend, Dr. Kessler?

Dr. KESSLER. That is correct. The Government will receive no patent rights. The gift is being made by Roussel Uclaf to the Population Council, without remuneration.

Chairman WYDEN. The Federal Government will not be party to any business decisions, including selection of manufacturers and distributors for the U.S. market?

Dr. KESSLER. The Government will not be part of any business decisions between the parties. We do have a responsibility and perhaps Ms. Pendergast can articulate how we view whether a manufacturer is qualified to produce a drug.

Ms. PENDERGAST. As part of any new drug application, the company that would like to market a drug in the United States must provide to us the chemistry and manufacturing information about how the drug will be produced. Before approving any marketing application, FDA investigators go to the manufacturing site and do an inspection. So, to that extent, we will be taking a look at whatever manufacturer there is, but we don't approve in advance who they might be willing to use.

Dr. KESSLER. Furthermore, Mr. Chairman, we also have responsibilities to make sure that a drug can be safely used once if it is approved, and once it is approved. We have responsibilities with regard to the distribution and the safe use. So, there is Government oversight of those conditions.

Chairman WYDEN. So in terms of the regulatory process, what you are talking about, Ms. Pendergast, is essentially the kind of

regulatory hurdle involving Government oversight of the manufacturing processes, the good manufacturing process requirement that is essential for any manufacturer who wants to produce this drug in the United States; is that correct?

Ms. PENDERGAST. That is correct. Those are our normal processes.

Chairman WYDEN. At this point, no one knows who that is going to be yet, because this is a decision to be made by the Population Council?

Ms. PENDERGAST. That is correct. Perhaps the Population Council knows, but we certainly do not.

Chairman WYDEN. Let me ask you one other question with respect to the agreement and where it stands in terms of specifics. In your opinion, Dr. Kessler, will the Population Council get everything they need as an organization to take this drug all the way through clinical trials and the approval process and not have to negotiate any more agreements with the company? Is it your view that they will get everything they need?

Dr. KESSLER. The Secretary and I and Ms. Pendergast expect that to be the case.

Chairman WYDEN. Doctor, we understand the clinical trials with this drug may start as early as this fall. Can you give us some baseline guidance as to how many locations and how many women may be involved?

Dr. KESSLER. The Population Council has an IND on file with the Food and Drug Administration. We have been told that they are planning to submit an amendment to that IND file. The information you are requesting would obviously be part of that IND file. We have been told by the Population Council that up in the range of about 2,000 women, they are expecting to design the clinical trial.

Chairman WYDEN. How long do you think the entire approval process might take? Again, I realize that this is an inexact part of the process, but in your opinion, how long do you think it might take for the approval process?

Dr. KESSLER. Let's define the word "approval." Let's talk about what needs to be done, what will be on the Population Council's clock, what will be on our clock. An application, the new drug application, needs to be submitted for the Agency to review.

We have been told by the Population Council that they anticipate that that application will take between 9 and 16 months to prepare. What needs to be done, besides collecting all the data, obviously an important part of that application, is having a manufacturing operation that is up and running. We cannot and we will not approve any application for which we are not confident that the sponsor can appropriately manufacture the drug. So, a significant part of that 9 to 16 months would be getting a manufacturing process up and running. That would not be on the Food and Drug Administration's clock.

I mean our clock starts when the application is submitted. We would anticipate, in part because we have seen a lot of preliminary data, there is still a lot we have not seen, but we would anticipate that approximately 6 months of actual approval time. We have

been told by the Population Council, that they expect to have clinical trials up and running by early fall.

There is an IND in effect, and our review time for an IND is usually less than 30 days.

Chairman WYDEN. Women often ask me how to speed up the approval process. They have waited a long time for a drug that 150,000 people around the world have used. The answer to this question is that the sooner the manufacturer is chosen, the sooner the process gets started. Is that correct?

Ms. PENDERGAST. That is right. I think the manufacturing process questions are the questions that will take the longest period of time.

Chairman WYDEN. One bit of housekeeping from yesteryear that I wanted to ask you about is what happens to the matter of RU-486 on the import alert list? As you know, I was very concerned about that years ago, because I always thought that import alerts were issued when there was evidence of a black market or somebody was smuggling it. When we went to ascertain what was behind the import alert, all we found was a bunch of letters in the file from organizations that said they thought that RU-486 was going to be the end of western civilization and it ought to be kept out. So, I am interested in the status of RU-486 on the import alert list. Doctor, maybe you could tell us what that is.

Dr. KESSLER. The import alert will remain in effect. The purpose of the import alert is to make sure that no counterfeit drugs or drugs of poor quality enter the United States.

Ms. PENDERGAST. It is not possible at this time for anyone to lawfully obtain Roussel Uclaf's RU-486 to bring it into the United States. So, at this time, were a woman to bring in what she thought was RU-486, the odds are it would be some sort of counterfeit or clandestinely manufactured drug of unknown safety. In addition, it is simply bad medical management for any woman to attempt to terminate a pregnancy medically by herself without very, very careful supervision of a physician.

Chairman WYDEN. I share that view, and I appreciate, Dr. Kessler, your concern about the counterfeiting. Because this subcommittee has certainly received reports about those prospects, over the years the bottom line is that the development process is moving forward. The days of foot dragging and stalling are over, the development process is moving forward, and I appreciate that.

In terms of where and when RU-486 might be used, and, again, absent the NDA from a sponsor, could you project, Dr. Kessler, at what stage of pregnancy this alternative might be available?

Dr. KESSLER. The studies that we consider the most relevant discuss the indication for use in the termination of early pregnancy, that is up to 49 days of amenorrhea, 49 days from the last period. It is important to point out that 49 days from the last period is really 21 days, 3 weeks, from the first missed period. Therefore it is the drug's usefulness, the drug's effectiveness, at least from the published studies is in the early stages of pregnancy. That means for the drug to be used, the diagnosis of pregnancy needs to be made very early on.

Chairman WYDEN. With respect to the first 49 days, I gather that that still accounts for a high proportion of the current pregnancy terminations. Is that right?

Dr. KESSLER. It has been estimated for example, in the French market, that it could represent as much as 20 or 25 percent of the pregnancy terminations market.

Chairman WYDEN. One other question, Dr. Kessler, and then I am going to recognize my good friend from Missouri for any questions he has. Doctor, from the standpoint of a physician, could you compare RU-486 using an antiprogestin like RU-486 to a surgical abortion? I think that would be helpful to have on the record, from the standpoint of advantages and disadvantages to physicians.

Dr. KESSLER. Let me just reiterate, Mr. Chairman, that obviously we need to review the application when it is submitted. Let me tell you what is known about surgical abortions and what are the risks, what are the advantages and disadvantages of the surgical abortion.

The risk of surgical abortion includes the risk of anesthesia, the risk of infection, the risk of injury to the cervix, and risk of uterine perforation. It is a surgically invasive procedure. The advantage to a surgical abortion over a medical regimen is that in fact, it could be done in probably less visits. It can be done quicker.

The advantage of a medical procedure is that the advantages of the medical procedure, obviously the complications of the surgical procedures such as uterine perforation, injury to the cervix, you would not see medically. The other advantage to the medical procedure is that, in fact, surgery usually, most people who perform abortions, wait later on, don't do the procedure in the early period of pregnancy. They wait. So, one of the advantages of the medical procedure is, in fact, that it could be done earlier.

There are advantages, there are disadvantages. Obviously, it awaits our full and thorough review to be able to give you a full answer.

Chairman WYDEN. But there is no requirement for anesthesia; is that correct?

Dr. KESSLER. There is no requirement for anesthesia. Certain surgical abortions are done with local anesthesia; others are done with more intense or general anesthesia.

Chairman WYDEN. Let me recognize my colleague from Missouri. We welcome him.

Mr. SKELTON. Thank you very much. As you know, Mr. Chairman, I have long had a very strong pro-life stance, but I do want to ask questions in regard to information I have that the chemical properties of this particular item is alleged to have a therapeutic value for a variety of other diseases, ranging from Cushing syndrome to memingioma, and also it deals with breast cancer. Would either one of you expand upon that for me, please?

Dr. KESSLER. There are investigational IND's that are in effect for the study of its use in other conditions. There are multiple IND's in effect. Some have been made public. As you know, we are not permitted to talk about IND's that have not been made public, but there is a range of conditions for which——

Mr. SKELTON. Well, there is a study, excuse me, it says major trials are underway to treat breast cancer. Can you speak of those, for instance?

Ms. PENDERGAST. That is correct, there are breast cancer trials being conducted in the United States, as well as trials for meningioma, Cushing's disease and other conditions.

Mr. SKELTON. Can you name any, other than those three?

Ms. PENDERGAST. It is also being studied for diabetes, endometriosis, and for, not in this country though, for ripening the cervix, for women who have completed their pregnancy and are actually going too long. It is being studied to bring a woman to labor better than the drugs that are now being used for that purpose.

Mr. SKELTON. Are any of those studies completed?

Dr. KESSLER. There is no I mean, again, we do not talk about those studies specifically, and whether an NDA has in fact, been submitted. That is confidential information.

Mr. SKELTON. Thank you, Mr. Chairman.

Chairman WYDEN. I thank my colleague. I very much appreciate him asking about the nonabortion uses, because I think we are going to see more and more of the drugs of the future in effect be these dual purpose drugs. They are going to be drugs that will be capable of attacking a wide variety of the cancers and the illnesses that my friend has mentioned. They are also going to be drugs that offer an alternative to surgical abortion. Of course, in our country people do differ on the abortion issue, as the gentleman notes.

One of the efforts of this subcommittee has essentially been to urge the evaluation of drugs by the book. The job of the gentleman who runs the Food and Drug Administration is to evaluate these drugs on the basis of their safety and efficacy. If they meet those standards, I feel that the American people want them. However, I know that the gentleman has strong pro-life views. He has always been a constructive member of this subcommittee and we are going to push hard for all safe uses of this drug. We appreciate the gentleman's questions.

Dr. Kessler, unless you have anything further that you would like to add, we will excuse you at this time. The subcommittee is working with you I think, on last count, on something like five issues at this point. You have always been very gracious, both with your time and with your staff's time to work with us. I know that this puts another huge issue on a plate that is already very full. We appreciate the way you are tackling this and look forward to working with you closely in the days ahead.

Dr. KESSLER. Thank you, Mr. Chairman.

Chairman WYDEN. We will excuse you at this time. Thank you, Ms. Pendergast.

Chairman WYDEN. Mr. Lester Hyman, Swidler & Berlin, representing Roussel Uclaf; Mr. James Boynton, Christie & Viener, representing the Population Council. If you all will come forward. You all have associates. Do you anticipate your associates possibly being involved with some of the questions, Mr. Hyman?

Mr. HYMAN. No, sir, one of my partners. This is John Hoff, who is a partner in the law firm as well.

Chairman WYDEN. Mr. Hoff, we know and we welcome him. Mr. Boynton, you have an associate as well?

Mr. BOYNTON. My partner, Karen Walker, who has been involved in this project.

Chairman WYDEN. Ms. Walker, if you and Mr. Hoff don't have any objections, let us swear you all as well as Mr. Boynton and Mr. Hyman at this time. Do any of you have any objection to being sworn as a witness?

[Witnesses sworn.]

Chairman WYDEN. We thank you for your cooperation. We know that you all have worked very, very long hours in order to make this day possible. I suspect, while most of America was enjoying a nice weekend, you all were cloistered in a room having discussions and negotiations. We appreciate how fast you have moved in recent days in particular to make this possible.

Why don't we begin with your statement, Mr. Hyman. We will make your prepared remarks a part of the record. Please proceed with any oral presentation you desire.

TESTIMONY OF LESTER HYMAN, SWIDLER & BERLIN, REPRESENTING ROUSSEL UCLAF

Mr. HYMAN. Thank you, Mr. Chairman. I hope that our red eyes prove the veracity of your statement about the work that all of us have devoted to this important project. I appear before you today as Washington counsel for Roussel Uclaf of France, one of the world's leading companies in the fields of human health, animal health and agricultural science.

Before answering your questions, I thought it would be useful for the subcommittee to have the benefit of some very important background information. To begin with, there is a widespread belief that the use of Mifepristone, which is the correct name of the compound that has become known popularly as RU-486, consists of a simple one-step process in which a woman swallows a pill and immediately terminates an early pregnancy. This is not the case.

Based on existing medical data, the entire procedure can be used only within the first 49 days after a woman's last period, which means, as you heard from Dr. Kessler, as a practical matter it can be used really during the first 3 weeks of a pregnancy. The party must undergo a physical or an ultrasound examination to verify her pregnancy, and confirm that it is within the permitted 7 week time span. Then she must take Mifepristone in a doctor's office or in a medical clinic, and stay there for about 2 hours.

Forty-eight hours later, she must return and take another pill, which incidentally is not a Roussel product, and there often is considerable pain attached to the procedure. In a number of cases, severe bleeding occurs, which must be carefully monitored, and sometimes treated with blood transfusion. Then the patient must return in a week to be sure that the procedure is complete.

There are many other problems, as well. For example, how does the distributor of the pill make certain that it is delivered only to medical personnel skilled in gynecology? What is to prevent a woman from taking the pill and then leaving the jurisdiction for another State, or even another country, and never turning up again for the second pill and the follow-up treatment? What if the woman changes her mind after taking the first pill? What happens if excessive bleeding takes place? Where does the woman go for treatment?

How do we prevent a black market from developing, whereby the pill becomes available outside a legitimate medical setting?

These are just a few of the myriad details that have required resolution before Mifepristone comes into the United States. Another question I often hear, and I believe, Mr. Chairman, you mentioned it yourself earlier on, since Mifepristone is available in France, England and Sweden, why isn't it available in the United States? If it is good enough for European women, it should be good enough for American women.

The answer to that question is quite complex, but it basically turns upon two points that relate to the specific situation in the United States. First, the European countries mentioned have much greater governmental control of doctors and clinics, especially in this field, as Mary Pendergast indicated earlier. So, it is easier to assure proper education, delivery and supervision of the procedure, than in the United States, where there is primarily a private and decentralized system of medicine and hospitals.

Another point is the fact that there is an ethical and emotional dispute in this country between the so-called pro-choice and pro-life groups, regarding the introduction of Mifepristone. Literally thousands of letters have been sent to our client demanding in the strongest possible terms either that the pill comes in or that the pill stays out. Ad to all of these the fact that in the previous administration the situation was precisely the opposite from where it is today.

Then President Bush spoke stridently against any procedure that would result in early pregnancy termination. In face of that opposition by the U.S. Government, Roussel decided not to bring Mifepristone into the United States. It was only when President Clinton changed the governmental policy and specifically asked Roussel to make the procedure available here, that our client, out of respect for the President of the United States, agreed to make every effort to comply with his request.

Extensive and protracted discussions have been held concerning a strictly controlled prescription and distribution system with appropriate labeling, so that basic procedures could protect the health and safety of American women.

As the result of our negotiations with the Population Council and consulting with the U.S. Government, I am pleased to state that Roussel Uclaf now has donated to the Population Council its U.S. patent rights on Mifepristone, not only for early termination of pregnancy, but also for the other medical uses that have been referred to here today such as labor induction, contraception, endometriosis, Cushing's syndrome, meningioma and breast cancer.

Roussel will receive no remuneration whatsoever, with the understanding that the company no longer will participate or be involved in the manufacture or the distribution of Mifepristone in the United States.

Finally, Roussel is pleased that it has been successful in granting the request of President Clinton by donating this important medical development for use by the women of the United States. My client particularly wants to thank you, Mr. Chairman, for your significant role in this ongoing process, and to stress its deep appre-

ciation to Secretary Shalala for her encouragement and assistance. That is the end of our statement.

Chairman WYDEN. Mr. Hyman, thank you very much. Again, my thanks to you for your cooperation over these many months. I will have some questions here in a moment.

Chairman WYDEN. Mr. Boynton, welcome. Please proceed.

TESTIMONY OF JAMES S. BOYNTON, CHRISTY & VIENER, REPRESENTING THE POPULATION COUNCIL

Mr. BOYNTON. Thank you, Mr. Chairman. I am testifying before you at the request of Margaret Catley-Carlson, the President of the Population Council. She is in Bangkok, Thailand, today, fulfilling a very important international commitment made many months ago, and she is very disappointed not to be here on this historic occasion.

I have been involved in the council's efforts to bring Mifepristone to the United States since 1991, and I would like to acknowledge at this point the very generous gift that Roussel Uclaf has now made to the Population Council, and also to express my own conviction that the council is now prepared to move forward to take the steps necessary to present the drug to the FDA in proper form for a decision by the FDA on its safety and efficacy. When and if approval is granted, the council will carry forward to make sure the drug is distributed in the United States in an appropriate fashion.

The council, it is important to emphasize, is a nonprofit, nongovernmental, nonpolitical scientific research organization, with a significant history. It is governed by a multinational board of trustees consisting of 20 women and men from 15 countries. Its mission is to improve the well-being and reproductive health of current and future generations around the world, and to help achieve a humane, equitable and sustainable balance between people and resources.

The council has been involved, as you know, Mr. Chairman, in a number of significant contraceptive products that are currently on the U.S. market. Particularly, the copper T intrauterine device, known as the ParaGard, that has been on the market since 1987, and another contraceptive of long lasting affect that you yourself mentioned earlier, NORPLANT, the culmination of a 22-year effort on the part of the council, extensive clinical testing and an enormously voluminous NDA.

The council's interest in Mifepristone dates back to 1982, when the first indications of its potential use in the human fertility area became known. The council's relationship with the inventor, Roussel Uclaf, predates that and goes all the way back to 1968. It has been a very productive relationship over the years, and I, again, wish to express the council's appreciation for this donation.

The council's interest in Mifepristone was originally based on its potential as a contraceptive. Having learned of the abortifacient application, which also is in the council's field of work, its interest currently is twofold.

First, belief that unsafe abortion is a major public health risk to women in developing countries, the primary focus of the council's mission, and concern that women in many countries, including the

United States, have access and the ability to choose a safe, effective method for early termination of pregnancy as an alternative to the surgical method.

Second, the council seeks to decrease the deaths and illness caused by unsafe abortion, and inherent in the risks of the surgical procedure. The council wants to ensure that if a woman makes the choice to terminate a pregnancy, an individual choice, that she will have the alternative of a less invasive or noninvasive medical alternative. But bottom line, from the council's point of view, it is hoped that when the FDA passes on Mifepristone for use in the United States, it will turn out to be an important stepping stone toward the availability of Mifepristone in the lesser-developed world.

Mr. BOYNTON. I am going to skip a fair amount of what is in my statement, if I could, simply to indicate that beginning last April with the announcement at the FDA of Roussel Uclaf's willingness to transfer rights to the Population Council, the council mounted a massive effort to begin to prepare for the steps that lie ahead.

Those steps include clinical trials expected to involve up to 2,000 American women, the preparation and filing of a new drug application for Mifepristone, the identification and selection of a manufacturer and distributor for the drug in the United States, and fundraising efforts.

Those efforts have involved a great portion of the council's personnel. Unfortunately, as the negotiations continued, it became necessary to put those efforts on hold in the fall. We have only recently been able to recommence the planning phase. We have a lot of important decisions to make. We will be working to make them as expeditiously as we can using good judgment, and we will be glad to keep your subcommittee informed of our progress in that regard.

We do expect that it will be possible to mount clinical trials once they have been designed in consultation with the FDA during the latter part of this year. It would be our hope, but at this point we can only express it as a hope because it is obviously subject to FDA approval of the new drug application, that it would be, as others suggested earlier, possible for the drug to be on the market in the United States sometime in 1996.

You had indicated interest in your comments in the way in which the drug will be prescribed and distributed in the United States, so I thought I might spend a moment running through some of those points.

The prescriber of the drug under the scheme we will be proposing to the FDA could be any licensed physician who is trained to assess the age of a particular pregnancy because the time period in which the drug can be properly administered is finite and who is trained to diagnose an ectopic pregnancy because it is important to exclude any ectopic pregnancies from this treatment method trained and authorized by law to perform surgical abortion, whether by Vacuum, aspiration, or D&C, and has access to a backup facility equipped for surgical abortion, resuscitation and blood transfusions, all of which are necessary emergency treatment should anything go wrong in the administration.

The locations in which Mifepristone will be proposed to be administered will include private physicians' offices as well as clinics

and hospitals. Again, so long as the private physician has access to a nearby facility able to provide emergency backup.

In terms of timing, the proposal will call for either three or four visits. The function of the first visit, which may be combined with the second, being to provide very complete information about the method, its contraindications, and potential side effects to make sure that before proceeding the woman has made a free choice to terminate her pregnancy and before the drug is administered to have an extensive informed consent form completed. All of this will be done in a fashion to protect the patient's confidentiality.

Within 36 to 48 hours of having taken the dose of Mifepristone, the woman will have agreed to return for a second dose of a prostaglandin which facilitates contractions to complete the abortion.

The woman will remain in the clinic setting for at least 4 hours to make sure that everything is going well and then will return for a follow-up visit 8 to 14 days later, at the end of which visit it will be expected that she will receive a medical discharge.

This is a serious procedure. It is an alternative to another serious procedure and we intend to design an administration procedure that fits the seriousness involved.

On behalf of President Catley-Carlson and Chairman MacGeorge Bundy and the other trustees of the Population Council, I would like to thank Roussel Uclaf for its generous gift of the United States rights to Mifepristone. The council intends to put those rights to good use and that includes the other indications as the preliminary research conducted to date is brought to fruition.

The council itself will focus its resources fulfilling its immediate mission, which is the introduction in the United States for the abortifacient application.

The council also thanks Secretary Donna Shalala of the Department of Health and Human Services and Commissioner David Kessler of the Food and Drug Administration and their respective staffs for their counsel in this process.

We would like to thank you, Chairman Wyden, and the subcommittee for holding this hearing and for your ongoing interest and concern in this subject matter. We look forward to the successful introduction of Mifepristone in the United States. Thank you very much.

[Mr. Boynton's statement may be found in the appendix.]

Chairman WYDEN. Well, thank you both. This truly is a historic day. A lot of us wondered if it was coming. I only have a few questions for you, but I want to thank both of you for your efforts, particularly for this around-the-clock set of negotiations you have had to make to be sure this got done by Monday morning, May 16, at 10 a.m.

Mr. Boynton, I will start with you regarding the drug's approval. It is obvious now that one of the real key issues is the selection and approval of a manufacturer. Where is the Population Council in this process? How soon do you anticipate making a decision on a manufacturer?

Mr. BOYNTON. We have received many indications of interest from a variety of companies. We have met with quite a number of the serious candidates, and we will continue that selection process.

Chairman WYDEN. Do you think this can be decided in 4 or 5 months?

Mr. BOYNTON. I would expect so.

Chairman WYDEN. Ftrankly, something that infuriated me over the years was this argument that there weren't any U.S. companies interested in any relationship with you or anybody else in terms of manufacturing this drug. Mr. Jenning, Director of the subcommittee staff and I were constantly contacted by people with real talent and expertise in the health and technology fields who said they were interested. It became apparent to me that there were going to be a lot of small businesses, small- and medium-sized businesses in particular that were very interested in a relationship with you or anybody else.

Could you tell the subcommittee for the record approximately how many contacts you have had from companies and firms here in our country that were interested in a relationship with you?

Mr. BOYNTON. It has been a long time since I have looked at the complete file, Mr. Chairman. I would estimate that number at about a dozen.

Chairman WYDEN. About a dozen.

Mr. BOYNTON. But I would also emphasize that interest is a far cry from actually possessing the very important expertise, financial backing, and good judgment that is necessary to make a successful introduction possible.

I would like, if I might, to recount a story that I was involved in on behalf of the Population Council in the mid1980's. You will remember that there was a product on the U.S. market called the Copper 7, which was withdrawn from the market in 1985 or 1986 in the wake of the Dalcon shield product liability debacle. The Population Council found its International Programs Division seeking to encourage use of the Copper T intrauterine device in the lesser developed world at a time when it was not present on the U.S. market.

To meet that challenge, we solicited indications of interest from what turned out to be very small companies, and I know that is a subject of interest to your subcommittee. We received about a half-dozen indications of interest, went through a careful screening process in which we were primarily concerned about the responsibility that would be evidenced in the marketing program for that device.

We ended up making the selection of a company known as GynaPharma, which successfully reintroduced the Copper T in the form of ParaGard to the U.S. market in 1987 and has had an excellent record because of the grave sense of responsibility that the people who make up that company have brought to the care of their distribution and marketing of the product. We are proud to be associated with them.

We would intend to repeat that exercise here, and I am confident that we will make a sound selection.

Chairman WYDEN. So at this point you have got about a dozen companies that you feel were serious and credible contacts, but given the process you just described, you could be hearing from quite a few more when your phone starts ringing off the hook later today.

Mr. BOYNTON. That is a possibility and we want to keep the decision open so we can receive those indications.

Chairman WYDEN. Let me ask you specifically on behalf of this subcommittee that you look very carefully at the proposals coming from small companies, because we feel in our country there are a whole host of small firms. I come from a State where virtually all the industry are small firms, small health technology and biotechnology companies. In fact, a lot of the contraceptive work. in our country is being done by firms of under 100.

So let me on behalf of the Small Business Subcommittee on Regulation, Business Opportunities, and Technology ask you to give special emphasis to reviewing those applications from small companies. Mr. Jenning, over the years, has heard from a lot of companies whenever there appeared to be some sign of formal action being taken. My guess is your phone is going to start ringing off the hook later today, and we have a special interest in those small firms being a part of your review.

Mr. BOYNTON. We will be glad to do so.

Chairman WYDEN. Let me ask you a couple of other questions with respect to how the process is going to be done.

You mentioned that there will be a dozen sites and about 2,000 women across the country. How do you anticipate advertising, recruiting or in some way getting the message out to women about these trials?

Mr. BOYNTON. Well, we will rely on the individual sites to recruit the volunteers for participation in the trials.

Chairman WYDEN. Now, will the women in the trials be charged for RU-486 or will they be paid for participating? What kind of financial arrangements do you anticipate between the women who participate and——

Mr. BOYNTON. A decision on that subject has not yet been made, Mr. Chairman.

Chairman WYDEN. What options are you reviewing in that regard?

Mr. BOYNTON. It really would be inappropriate for me to comment at this time.

Chairman WYDEN. Fair enough. Fair enough.

Let me turn, now, to you, if I could in fact, let me mention one other point that you touched on, Mr. Boynton, and I commend you for it. That point was regarding doctors' offices, where their views really address these serious health and safety questions.

I think what the Food and Drug Administration indicated to us really complements your comments. The FDA is going to be looking particularly at doctors who do this procedure in their office having admitting privileges in a nearby hospital so that there is some relationship between doing a procedure in the office and having hospital privileges nearby. So, I think it complements the comments you have made, and I commend you for it.

Let me turn to you, if I could, Mr. Hyman. Again without getting into the details of the agreement, can you assure the subcommittee that with this patent transfer in effect the Population Council has everything it needs from Roussel to take this product through approval and into commercialization?

Mr. HYMAN. We can assure the subcommittee that that has taken place.

Chairman WYDEN. Well, that is very welcome news. I think people have been concerned that there were going to have to be further negotiations at some other point in order to actually get this job done. What you have just assured this subcommittee and me, Mr. Hyman, is that this is the end of the road, that you all have transferred to the Population Council what they need. To me, that is a signal that the days of delay, stonewalling and lawyers are on their way to an end, and women are going to get access.

Mr. HYMAN. I don't have to agree with the last point that the role of lawyers has come to an end, do I?

Chairman WYDEN. I suspected that that might be the case, and this will liberate you to pursue other things.

Mr. HYMAN. Thank you, sir.

Chairman WYDEN. I am sure they will be constructive as well.

This subcommittee has been at this matter for 4 years and you all have been working with us for a good portion of it. An awful lot of staff people worked very, very hard to make this day possible and I want to single out a few of them.

Mary Pendergast, Deputy Commissioner at the Food and Drug Administration, has done yeoman's work. In terms of the various staff matters on this issue, Diane Thompson, the Congressional Affairs Director at the Food and Drug Administration, in my view, also deserves commendation for her work, as well as Carol Heppe of Congressional Affairs. We also want to commend Jerry Klepner, the Assistant Secretary for Legislation at the Department of Health and Human Services, for all the work he did. I personally think, as I think you all know, but American people ought to know, that this fellow sitting on my right, Mr. Steven C. Jenning has done as much as anybody to make this possible, having staffed this now for 4 years. He, too, deserves, in my view, great credit.

Let me say finally in concluding this hearing that the American people should make no mistake at all about why we have been able to reach this point. That fact is very simply that President Clinton and Secretary Shalala intervened and said that American women ought to have access to all safe and effective health services. They said it wasn't right to evaluate this drug on the basis of politics. We are here today in a position to get this drug through the commercialization process because of the extraordinary and exceptional commitment of the President of the United States and Secretary Shalala.

The rest of us have had an interest in this matter for a lot of years, but it would not have happened without the President of the United States and without Secretary Shalala. In my view, this country, women and our families owe them a special debt of gratitude.

Unless you have anything to add further, we are going to excuse you. In fact, excuse me. Our counsel, very able counsel from the Minority side, I want to apologize to him for this omission. He had a question that he wanted to pose that is in an important area. Let me recognize him at this point.

Mr. LEHMAN. I appreciate the Chairman's indulgence. You mentioned about lawyers and Dalcon shield and that was one area I

wanted to ask about since we haven't seen the agreement and we did understand the Population Council does receive a significant amount of its funding through taxpayer funding.

Under the agreement, who would have liability exposure? Would the Population Council or the manufacturer you choose?

Mr. BOYNTON. When we select a manufacturer-distributor, we will negotiate an appropriate indemnification package with them, as we have in all other transactions in which we have been involved.

Mr. LEHMAN. Is it possible you might have some exposure?

Mr. BOYNTON. It is possible in the clinical trial phase, but it will be limited.

Mr. LEHMAN. Thank you. Thank you, Mr. Chairman.

Chairman WYDEN. Gentlemen, unless you all have any further comments you would like to offer the subcommittee, we will excuse you. The subcommittee is adjourned.

[Whereupon, at 11:28 a.m., the subcommittee was adjourned, subject to the call of the chair.]

APPENDIX

OPENING STATEMENT
REP. RON WYDEN

BEFORE THE SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES AND TECHNOLOGY

RU 486: STATUS REPORT ON THE U.S COMMERCIALIZATION PROJECT

May 16, 1994

Today, the Subcommittee on Regulation, Business Opportunities and Technology will continue its oversight of government efforts to assist American pharmaceutical companies in the development and commercialization of anti-progestin drugs.

This important new line of drugs includes RU 486, the French abortifacient therapy that also shows promise for treating a variety of conditions and diseases threatening the health of many Americans.

Our focus, today, is the status of negotiations now proceeding in New York to license RU 486 to the non-profit foundation, the Population Council.

> It is my view that this licensing negotiation...now well into its second year...offers the best hope for American women to have a safe, effective alternative to surgical abortion before the end of this century.

Delays in concluding this negotiation, therefore, have been extremely troubling. Now, finally, the Population Council and Roussel Uclaf, the manufacturer, have come to an agreement to bring this drug to the United States.

> This is an extraordinary victory for American women. We are turning away from a time when women trying to bring this drug into the United States were the subject of stop-and-frisk searches by U.S. border guards.
>
> Today, medical science is finally winning out over politicized science.

RU 486 will get a fair and dispassionate analysis by the Food and Drug Administration. I believe that within two years, those tests will lead to approval by our government and the general distribution of the drug.

For almost four years, this subcommittee has been following the debate over the introduction of RU 486 in the United States. Along with a detailed investigation of the safety and efficacy of this product in foreign markets, our inquiry has questioned whether the previous presidential administration actively discouraged the introduction of this product in this country.

The resulting controversy has...for better or worse...transformed this pharmaceutical into a lightning rod in the abortion debate. Although an important new medical agent in its own right, this drug's political symbolism has very nearly overshadowed its pharmacological importance.

Very clearly, RU 486 told a story about the kinds of political problems dual-use drugs like this may face in the future. Here is a pharmaceutical used widely in Europe as an abortifacient. But its chemical properties also seem therapeutic for a variety of diseases and other conditions ranging from Cushing's Syndrome to meningioma.

> In the United States, major trials are underway to treat breast cancer with RU 486, and also to use the product as a morning-after contraceptive.

We face a choice. Should we exile an important new product, an agent that could have many strong therapeutic values, based on the fact that one of the drug's uses fails to pass one political litmus test? Or should we use good sense and good judgement to manage our health product development activity, including our regulation of new drugs and devices?

I am convinced that this drug's controversial history lead to its placement on the import alert list, a decision leading to the now famous search-and-seizures. The cascading political fallout generally had a debilitating effect on a variety of medical experimentation with RU 486 in the United States.

The agreement announced today reverses this unwholesome development.

It sends a strong statement to the international medical and pharmaceutical community that the United States government is committed to a seachange in attitude.

Witnesses coming before this subcommittee today will offer (1) the first detailed explanations of the clinical trials leading to the likely approval of this drug, (2) the partnerships which will be built between small manufacturers and distributors to bring this drug to market, and (3) the probable ways and means of access to this therapy by American women who choose RU 486 over surgical abortion.

We welcome Dr. David Kessler, commissioner of the Food and Drug Administration, who will explain the regulatory process for this drug over the next two years.

Primary to this process is the degree to which Dr. Kessler will weigh clinical experience with this drug in Europe, where more than 150,000 women have used RU 486 since the late 1980s.

Also, the FDA will have the challenging task of assessing the development of a medical practice system for administration and supervision of RU 486. Here the differences between the French health care system and our own will have to be rationalized so that RU 486 has the widest possible availability with the strongest possible safety protections.

The French system is government owned and operated.

Our own is a mixture of public and private hospitals, religious and secular, profit and non-profit.

Sponsors of this drug will have to develop a consistent medical management system, including standards of practice, that will make the delivery of this drug as safe and effective as the drug, itself.

Mr. James Boynton, representing the Population Council, will explain the logistics of the clinical trials. Of greatest interest to the Chair will be the restrictions and requirements for use of this drug. Will RU 486, for example, be limited to hospital use, only, or will women have the opportunity to choose this therapy in the privacy of their own doctor's offices?

Finally, the subcommittee welcomes Mr. Lester Hyman, representing Roussel Uclaf. Mr. Hyman and Mr. Boynton have labored long and hard to conclude this important licensing agreement, and they have our congratulations.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

DAVID A. KESSLER, M.D.

COMMISSIONER

OF

FOOD AND DRUGS

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES,

AND TECHNOLOGY

COMMITTEE ON SMALL BUSINESS

U.S. HOUSE OF REPRESENTATIVES

MAY 16, 1994

TO BE RELEASED ONLY UPON DELIVERY

Mr. Chairman, the Food and Drug Administration (FDA) has encouraged the submission of a new drug application (NDA) for mifepristone, commonly called RU-486, for interruption of early pregnancy so that we can determine whether it is safe and effective for that indication. If there is a safe and effective medical alternative to any surgical procedure, American women should have access to that drug regimen. We cannot form, however, any definitive conclusions about the drug's safety and effectiveness, or approve it for marketing in the United States, without first reviewing the studies and other data that would be submitted in a new drug application.

On January 22, 1993, President Clinton executed a memorandum to the Secretary of Health and Human Services directing her to assess initiatives to promote the testing and licensing in the United States of RU-486. In response, FDA's efforts have been focused on encouraging and facilitating the submission of an NDA.

Immediately after the President issued the memorandum, I wrote to Dr. Edouard Sakiz, President of Roussel Uclaf, and requested a meeting to discuss the possible therapeutic uses of anti-progestational drugs and, in particular, FDA's interest in receiving an NDA for RU-486 for interruption of early

pregnancy. Both the Secretary and I also let Hoechst AG, Roussel Uclaf's parent corporation, know of our interest.

On February 24, 1993, senior representatives of FDA and Roussel Uclaf met to discuss the clinical and manufacturing data on the drug that FDA would need to review as part of an NDA for an abortifacient indication. At that meeting, FDA received a strong commitment from Dr. Sakiz that he would find a way to bring RU-486 to the U.S. market. Dr. Sakiz stated that Roussel Uclaf would not be directly involved, but instead would work through a third party in the United States. Dr. Sakiz also committed to making the drug available for research on other potential uses. FDA and Roussel Uclaf agreed to continue to work on this matter until remaining issues could be resolved.

At an April 20, 1993 meeting at the FDA, Roussel Uclaf indicated its willingness to modify its 1982 contract with the Population Council, a non-profit scientific and technical organization. These modifications would permit the Population Council and its sublicensees to produce, test, and distribute RU-486 in the United States. The Population Council agreed to work to identify a manufacturer for RU-486 for the United States market and to begin a clinical trial to test the drug in the United States.

At that point, we thought that clinical trials on RU-486 would begin soon in the United States. This proved not to be the case. Before the Population Council would begin clinical trials, the Population Council and Roussel Uclaf undertook complex negotiations pertaining to the transfer of the RU-486 patents and the basis for distribution of the drug in the United States. After a year of these negotiations, on April 14, 1994, the Secretary and senior Department officials met with the heads of Roussel Uclaf and the Population Council.

At that meeting, the parties indicated their willingness to continue their negotiations, and the Secretary made it clear to the negotiating parties that agreement on all outstanding issues should be reached no later than by May 15, 1994.

We are pleased that Roussel Uclaf and the Population Council have concluded their negotiations, and that Roussel Uclaf has donated the patents on RU-486 without remuneration. We anticipate that the Population Council will now pursue the clinical testing of RU-486 in the United States. We will work with the Population Council to make certain that their clinical trials are well-designed and carefully conducted, in order to provide useful information on how the drug might be properly used in this country. We also understand that the Population Council will file a new drug application for RU-486. We will

review it carefully under the appropriate medical and scientific criteria.

It should be recognized that the termination of a pregnancy is not a simple procedure, whether it is done surgically or through a medical regimen. Women should not think that pregnancy termination using a medical regimen will be simple. It will not be. In Europe, where RU-486 has been used in over 150,000 women, the procedure requires several visits to a medical facility, a precise dosing scheme using two different drugs, and close monitoring to care for women who may experience excessive bleeding or other complications. We anticipate that any use of RU-486 in the United States would have to follow the same type of strict distribution and use conditions.

TESTIMONY OF THE POPULATION COUNCIL, INC.
BY JAMES S. BOYNTON, COUNSEL

UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON SMALL BUSINESS

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY

16 May 1994

My name is James S. Boynton; I am a member of the New York City law firm of Christy & Viener, counsel to The Population Council, Inc. (the "Council"). I am testifying before you at the request of Margaret Catley-Carlson, the President of the Council who is in Asia this week fulfilling an important international commitment and unfortunately unable to be present herself. I have represented the Council in a wide variety of commercial licensing and related matters since the early 1980's.

I have been closely involved in the Council's efforts to bring mifepristone (RU 486) to the United States since 1991 and have participated in all of the negotiations with representatives of Roussel Uclaf, S.A. ("Roussel") and its parent company, Hoechst, A.G., since our meeting with Commissioner Kessler of the Food and Drug Administration and members of his staff in April 1993 resulted in a commitment from Dr. Edouard Sakiz on behalf of Roussel to license mifepristone to the Council.

A. Background Information on the Council

The Council is a nonprofit, nongovernmental research organization established in 1952. It is governed by a multinational Board of Trustees consisting of 20 men and women from 15 countries. Its New York headquarters supports a global network of regional offices in Bangkok, Cairo, Dakar, Mexico City and Nairobi and country offices in 11 additional countries.

The Council seeks to improve the well being and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources. The Council:

- analyses population issues and trends;

- conducts biomedical research to develop new contraceptives;
- works with public and private agencies to improve the quality and outreach of family planning and reproductive health services;
- helps governments to influence demographic behavior;
- communicates the results of research in the population field to appropriate audiences; and
- helps build research capacities in developing countries.

As background to the Council's involvement with mifepristone, the Council, through its Center for Biomedical Research, has developed six reversible, long-acting contraceptive methods now in use worldwide. These include NORPLANT® levonorgestrel implants; NORPLANT® II implants, an improved version that will soon be introduced in the United States; a levonorgestrel-releasing intrauterine device; and three copper intrauterine devices (TCu200B, TCu220, TCu380A), the most advanced of which (TCu380A) is currently marketed in the United States under the name ParaGard®.

The Council is currently developing several other new methods of contraception including a single-implant system for women; a two-implant system for men; several contraceptive rings; transdermal contraception; a microbicide that will allow women to protect themselves from sexually transmitted diseaes including AIDS; a contraceptive vaccine for men; and hormone delivery systems for a variety of reproductive disorders.

B. Council's Involvement with Mifepristone.

The Council's interest in mifepristone is two-fold: belief that unsafe abortion is a major public health risk to women in developing countries, and concern that women in many countries, including the United States, are being deprived of a safe, effective method for early medical termination of pregnancy. The Council seeks to decrease the deaths and illness caused by unsafe abortion. We want to ensure that, if a woman opts to have an abortion, the procedure or regimen is safe for her. The Council supports giving women contraceptive options; with mifepristone, women also will have a choice of abortion methods. In addition, attempting to obtain approval of mifepristone in the United States will be an important step toward making this abortion method available in developing

countries in which abortion is legal and a safe system of administration can be insured.

In 1982, the Council entered into discussions with Roussel, the developer of the mifepristone compound, concerning the possibility of conducting pre-clinical and clinical studies on mifepristone in the United States of the type that could be useful in obtaining approval of a New Drug Application in the United States or comparable approvals in other countries. An Agreement, dated as of September 1, 1982 (the "Agreement"), between the Council and Roussel resulted. Reflecting an important Council mission to expand contraceptive options in developing countries, the Agreement contemplated that Roussel would provide products resulting from research on mifepristone to public sector organizations in all countries of the world except Australia, Canada, Europe, Japan, New Zealand, South Africa and the United States. In 1984 the Agreement was amended to include the United States. The Council began such studies in 1982 and they continued until 1989. As required by the Agreement, the Council reported the results of the studies to Roussel.

Following the controversy associated with the approval of mifepristone by the French government in 1988, Hoechst AG, the parent company of Roussel, decided to limit distribution of this drug. As a consequence, clinical trials in the United States were discontinued in 1989 and the Council was informed the drug would not be distributed in North America.

In 1991 the Council received indications from Roussel that it would favor the conduct of further trials in the United States leading to filing a New Drug Application with the Food and Drug Administration and distribution to the public sector in the United States. The Council pursued discussions with Roussel through the beginning of 1992 only to learn that introduction of mifepristone in the United States would not be permitted.

Beginning in 1988 the Council developed a plan for acceptability studies of mifepristone in China, Cuba and India; these studies have since been completed and the results will soon be published. An acceptability study is also underway in Vietnam.

C. Abortion in the United States

Each year, there are 1.6 million surgical abortions in the United States, 89% performed in the first trimester. Although abortion is legal in this country, access to it is limited and it is difficult for some women to obtain: because they cannot afford the cost and government will not pay for it; because many states have only a few abortion clinics and women must travel great distances to get to them; and because there is a shrinking pool of providers to staff the clinics. Restrictions designed to delay or discourage abortions have been passed by half the states. Abortion clinics have been picketed, women seeking abortions have been harassed and intimidated, and providers have been stalked at work and in their homes. The situation in the United States is in stark contrast with that in France, the United Kingdom, and Sweden, where abortion is legal and widely available and where mifepristone is an option.

With mifepristone, the U.S. situation would be changed:

- American women would have a choice of abortion methods: early medical induction via a mifepristone/prostaglandin combination, and surgical, either by vacuum aspiration or dilatation and curettage.

- Abortions could be performed within 49 days of amenorrhea, earlier than surgical abortion is usually performed.

- Qualified physicians who eschewed performing surgical abortions could administer mifepristone, so long as good medical care was available in case of emergency and surgical abortion could be provided when required.

While the Council is pleased to be able to facilitate the introduction of mifepristone in the United States, it is important to remember that this is but one step toward making mifepristone available in lesser developed countries around the world where population and female health issues are pressing.

D. History of the Current Negotiations

Against this background when President Clinton asked in January 1992 that Roussel make mifepristone available in the United States, it was natural for the Council to become involved. After the meeting held at the offices of the Food and Drug Administration on April 20, 1993 involving Dr. David Kessler of the FDA and several members of his staff, Margaret Catley-Carlson and other officers of the Council and myself

and Dr. Edouard Sakiz and Catharine Euvrard of Roussel, negotiations began promptly. The principal events in the negotiations were as follows:

May 4	Initial meeting with counsel.
June 29	Contract negotiating session in New York.
August 2	Counsel for the Council meet with FDA to discuss progress.
August 5	Council delivers new draft of contract to Roussel.
September 13	Roussel presents revised version of contract to the Council.
October 4	Counsel comments on revised contract.
October 14	Dr. Sakiz and Ms. Catley-Carlson meet on contract.
November 13	Counsel sends revised contract to Roussel.
November 29	Meeting of principals and counsel in Paris.
December 2	Council delivers new revised version of contract.
December 31	Lawyers for both parties meet in New York.
February 14, 1994	Principals and counsel meet in Paris.
April 12	Principals and counsel meet in New York.
April 14	Principals and counsel meet with Secretary Shalala and Commissioner Kessler in Washington.
April 29	Counsel meet in Washington to review FDA issues.
May 5	Counsel and scientists meet with FDA staff.

At each stage of the negotiations the Council has pressed for faster progress and has been ready, willing and able to conclude the negotiations. We are delighted that a successful conclusion has now been reached.

E. Council Preparations

As negotiations commenced in May 1993, the Council launched a massive effort to plan and prepare for clinical trials involving 2000 American women, the preparation and filing of a New Drug Application for mifepristone, the identification of a manufacturer and a distributor for mifepristone in the United States and fund-raising to support the expense of these efforts. In the process, among other activities, Council personnel:

- consulted with representatives of women's health groups, family planning and service providers, other medical experts and public affairs specialists at four separate meetings

- consulted with the Council's existing group of international public health experts

- created a Medical Advisory Board for mifepristone consisting of 10 experienced specialists in obstetrics/gynecology and abortion providers

- distributed a questionnaire to several dozen investigators and clinic personnel who have expressed interest in participating in the clinical trial

- made preliminary agreement with a contractor to monitor the clinical trial

- collected proposals from companies interested in acting as manufacturer and/or distributor for mifepristone in the United States

- held preliminary discussions with many of those which have submitted proposals

- consulted widely on the appropriate delivery system for mifepristone in the United States

- reviewed data from the French, English and Swedish clinical studies

- consulted with potential donors

Based on the activities to date, the Council believes that it will be possible to complete clinical trials and the New Drug Application and to select appropriate companies to act as manufacturer and distributor in the United States. I have no misgivings about the Council's ability to complete this mission with due regard to the public interest and the safety of those who elect to use mifepristone in the United States in the future.

On behalf of President Margaret Catley-Carlson and Chairman MacGeorge Bundy and the other 19 Trustees of the Population Council, I thank Roussel Uclaf for the generous gift of the U.S. rights to mifepristone; the Council intends to put the rights to good use. The Council also thanks Secretary Donna Shalala of the Department of Health and Human Services and Commissioner David Kessler of the Food and Drug

Administration and their respective staffs for their counsel, and Congressman Wyden and the Subcommittee for holding this Hearing and showing interest and concern. The Council looks forward to successful introduction of this method in the United States.

The Population Council

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News Release

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FOR IMMEDIATE RELEASE
16 MAY 1994

The Population Council Announces Receipt of Mifepristone (RU 486) Rights from Roussel Uclaf for the United States

WASHINGTON--The Population Council announced today (May 16, 1994) the transfer without remuneration of the US patent rights for mifepristone (RU 486) from Roussel Uclaf to the Council. This transfer of rights will enable the Council to select a manufacturer and a distributor for mifepristone, conduct clinical trials, and file for regulatory approval of mifepristone for marketing.

Roussel is transferring the rights to mifepristone in the US, not only for abortion purposes but for all medical indications for the drug, without any remuneration. The Council or a subsidiary will license the manufacturer/distributor for the abortifacient indication, while the remaining rights will be developed separately.

Margaret Catley-Carlson, president of the Population Council, said in a statement, "We are exhilarated and extremely gratified that these extended negotiations have ended successfully. We will proceed quickly to do what is necessary to prepare the file for submission to the US authorities."

Phase II clinical trials of mifepristone alone were conducted by the Population Council at the University of Southern California in Los Angeles and other clinics outside the US from 1983 to 1989, to test safety and tolerance, dosage and effectiveness, and usefulness as a contraceptive. Beginning in 1988, the Council developed a plan for acceptability studies of mifepristone in several developing countries; these studies have since been completed and publication is anticipated later this year.

The Population Council must apply to the FDA to amend its current Investigational New Drug (IND) permit to include the protocol for a clinical trial, including locations. At present, a trial is contemplated of upwards of 2,000 women volunteers at a number of sites around the country. The Council also has taken preliminary steps toward submission of the New Drug Application (NDA) to the FDA and has started reviewing data from the French, British, and Swedish studies.

The Population Council One Dag Hammarskjold Plaza, New York, New York 10017

Statement by Margaret Catley-Carlson
President of the Population Council
16 May 1994

Delivered by James S. Boynton, Christy & Viener
Counsel, The Population Council

"We at the Population Council are exhilarated and extremely gratified that these extended negotiations have ended successfully and that American women will have access to mifepristone as a safe and effective medical abortion option. I regret that a long-standing and important international obligation in Asia prevents me from delivering this statement in person.

"The Council will proceed quickly to do what is necessary to prepare the file for submission to the US authorities. We are confident we will be able to arrange for manufacture and distribution in the US. We plan to move quickly to arrange for financing, insurance, manufacture and distribution so that all will be in place by the time we receive FDA approval.

"We are grateful for the patience and good will of medical, pro-choice, and women's organizations during the lengthy negotiations, when a successful conclusion appeared to be elusive. And we thank the people in Health and Human Services and the Food and Drug Administration, particularly Secretary Shalala and Commissioner Kessler and their staffs for their counsel, and those in the Congress, especially Congressman Ron Wyden, for their steadfastness and concern.

"The Council has sought to bring mifepristone to the US, not to increase the incidence of abortion, but to provide a choice of safe abortion methods. We want to ensure that, if a woman opts to have an abortion, the procedure or regimen is the safest and most acceptable for her. We support giving women contraceptive options; with mifepristone, women also will have a choice of abortion methods."

The Population Council One Dag Hammarskjold Plaza, New York, New York 10017

The Population Council and Mifepristone

The Population Council seeks to improve the wellbeing and reproductive health of current and future generations around the world, and to help achieve a humane, equitable, and sustainable balance between people and resources. The Council, a nonprofit, nongovernmental research organization established in 1952, has a multinational Board of Trustees; its New York headquarters supports a global network of regional and country offices.

The Council's work encompasses the social, health, and biomedical sciences. The Council ■ analyzes population issues and trends; ■ conducts biomedical research to develop new contraceptives; ■ works with public and private agencies to improve the quality and outreach of family planning and reproductive health services; ■ helps governments to influence demographic behavior; ■ communicates the results of research in the population field to appropriate audiences; and ■ helps build research capacities in developing countries.

Our interest in mifepristone is two-fold: belief that unsafe abortion is a major public health risk to women in developing countries, and concern that women in many countries, including the United States, are being deprived of a safe, effective method for early medical termination of pregnancy. We seek to decrease the deaths and illness caused by unsafe abortion. We want to ensure that, if a woman opts to have an abortion, the procedure or regimen is safe for her. We support giving women contraceptive options; with mifepristone women also will have a choice of abortion methods. In addition, registration of mifepristone in the United States would be an important gateway to access around the world.

The Population Council began research on mifepristone soon after its discovery in 1982 by scientists at the French pharmaceutical company, Roussel Uclaf. The Population Council obtained an IND for clinical testing of safety and efficacy in 1983 and negotiated a joint development agreement with Roussel in 1984. For six years, the Council collaborated with Roussel on clinical and basic research on mifepristone in the United States, in Europe, and in developing countries. These studies showed that administration of mifepristone alone produced abortion during the first few weeks of pregnancy in from 60 to 85 percent of women, depending on length of gestation; when administered with another drug, a prostaglandin, the effectiveness of mifepristone was increased to 96 percent. In addition, beginning in 1988 the Council developed a plan for acceptability studies of mifepristone in India, China, and Cuba; these studies have since been completed and results will be published. An acceptability study is also underway in Vietnam.

Now that Roussel has transferred the US patent rights for mifepristone to the Council, we will proceed quickly to conduct clinical trials, select a manufacturer and a distributor, and do what is necessary to prepare the file for submission to the Food and Drug Administration. The Council is eminently qualified to take on the challenge of bringing mifepristone to American women. Council scientists have developed six reversible contraceptive methods: three models of the Copper T IUD, the levonorgestrel-releasing IUD, NORPLANT® implants and NORPLANT® II rods. We are currently developing a single-implant system for women, a two-implant system for men, contraceptive vaginal rings, a transdermal contraceptive, a contraceptive vaccine for men, and a microbicide women can use to protect themselves against sexually transmitted diseases, including AIDS.

May 1994

EARLY TERMINATION OF PREGNANCY WITH MIFEPRISTONE (RU 486) AND THE ORALLY ACTIVE PROSTAGLANDIN MISOPROSTOL

RÉMI PEYRON, M.D., ELISABETH AUBÉNY, M.D., VÉRONIQUE TARGOSZ, M.D., LOUISE SILVESTRE, M.D., MAGUY RENAULT, FRANÇOIS ELKIK, M.D., PHILIPPE LECLERC, PH.D., ANDRÉ ULMANN, M.D., PH.D., AND ETIENNE-EMILE BAULIEU, M.D., PH.D.

Abstract *Background and Methods.* The combination of mifepristone (RU 486) and a prostaglandin analogue given either intramuscularly or intravaginally is effective in terminating early pregnancy, but the prostaglandin component of the regimen is cumbersome to administer and has side effects. We conducted two studies to determine the efficacy of 600 mg of mifepristone followed by a small dose of misoprostol, an orally active prostaglandin E_1 analogue, for the same purpose. In the first study, 505 women who had had amenorrhea for less than 50 days received 400 μg of misoprostol 48 hours after receiving mifepristone, if the pregnancy was not terminated within that period. In the second study, 390 women initially received the same treatment, but if the pregnancy was not terminated within four hours after the administration of misoprostol, they were offered an additional 200-μg dose of misoprostol.

Results. In study 1, the rate of success (termination of pregnancy and complete expulsion of the conceptus) was 96.9 percent (95 percent confidence interval, 94.1 to 97.7 percent) — similar to the success rate of approximately 95 percent for mifepristone followed by the intramuscular or intravaginal administration of prostaglandin. Abortion occurred in 2.9 percent of the women within 48 hours after the administration of mifepristone, in 60.9 percent within 4 hours after the administration of misoprostol, and in 33.2 percent thereafter. The failures included ongoing pregnancies in four women (0.8 percent) and incomplete abortions in nine (1.8 percent); two other women (0.4 percent) required vacuum aspiration for prolonged uterine bleeding. In study 2, pregnancy was terminated in 5.5 percent of the women before the administration of misoprostol and within four hours after the first dose of misoprostol in 69.1 percent. Among the 71 women who received a second dose of misoprostol, 67 had complete abortions, 2 had partial retention of the conceptus, 1 had synechia with ongoing pregnancy, and 1 had an ectopic pregnancy. One ongoing pregnancy, which was terminated by vacuum aspiration, was recorded among the 27 women who declined to take the second dose of misoprostol. The overall rate of success of the regimen with the optional second dose of misoprostol was 98.7 percent (95 percent confidence interval, 96.8 to 99.5 percent). No woman had any serious adverse event.

Conclusions. The combination of mifepristone and misoprostol is effective for the termination of early pregnancy in terms of success, tolerance, safety, and practicality. (N Engl J Med 1993;328:1509-13.)

MIFEPRISTONE (RU 486) is a potent antiprogestin, but when it is administered alone in early pregnancy, termination of the pregnancy is incomplete in 20 percent or more of women.[1-3] This relative lack of efficacy may be due to an insufficient increase in the prostaglandin concentration in the uterus to allow completion of the abortion.[4,5] The efficacy of prostaglandin to complement the antiprogesterone effect of mifepristone for the voluntary termination of early pregnancy is well established.[4,6-9] The rationale for the sequential administration of the two drugs[4,5] is that the prostaglandin analogue increases uterine smooth-muscle contractility[10,11] beyond that which results from the ability of mifepristone to inhibit progesterone action and to increase endogenous prostaglandin concentrations.[12,13]

In France, sulprostone, a prostaglandin E_2 derivative (250 μg administered intramuscularly 36 to 48 hours after the administration of 600 mg of mifepristone), has been used for the voluntary termination of pregnancy in women who have had amenorrhea for less than 50 days.[8,9,14] Less often, gemeprost, a prostaglandin E_1 derivative, has been given intravaginally[8,9]; in Great Britain gemeprost is used to terminate pregnancy in women who have had amenorrhea for less than 63 days.[6,15] Myocardial infarctions attributable to coronary spasm, one of them fatal, have occurred in 3 of the more than 60,000 women given sulprostone.[9,16] As a result, its use has been abandoned. Currently, termination of pregnancy with mifepristone and any prostaglandin should not be undertaken in any woman who is older than 35 years or is a heavy smoker.

The oral administration of a prostaglandin should improve the mifepristone–prostaglandin method by

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increasing safety, convenience, and potentially, privacy. Unlike prostaglandin E_2,[17] 9-methylene prostaglandin E_2 complements the action of mifepristone in the termination of early pregnancy,[18] but it is not commercially available. The oral administration of 400 μg of misoprostol, a prostaglandin E_1 derivative,[19] 48 hours after the administration of 600 mg of mifepristone is also effective for this purpose.[20] Among 100 pregnant women who had had amenorrhea for less than 50 days, the success rate was 95 percent, indicating that misoprostol, although not an efficient abortifacient when taken alone,[21] is very active when given after mifepristone.

We describe here the results of two studies of the termination of pregnancy with mifepristone and misoprostol. In the first study, conducted at the request of the French Ministry of Health, we tested mifepristone and a single dose of misoprostol. In the second study, an additional dose of misoprostol was offered to women who had not aborted four hours after the first dose of misoprostol.

Methods

The study protocols were approved by the Délégation à la Recherche, Assistance Publique–Hôpitaux de Paris, and the Comité d'Ethique, Hôpital Broussais, and written informed consent (including acceptance of surgical evacuation in case of treatment failure) was given by all study subjects. Voluntary termination of pregnancy is legal in France during the first 84 days of amenorrhea, but the medical method is currently allowed only up to day 49. Pregnancy must be confirmed by measurement of the serum concentration of the beta subunit of human chorionic gonadotropin (β-hCG) or ultrasonography.

The exclusion criteria for the two studies were as follows: age greater than 35 years, amenorrhea for more than 49 days, a possibility of ectopic pregnancy, ongoing spontaneous miscarriage, a concomitant blood-clotting abnormality, smoking more than 10 cigarettes per day, asthma, and cardiovascular or other serious disorders.

Study 1, conducted from June through October 1991, involved 505 women at 25 centers. Their mean (±SD) age was 26±5 years. On the first day, mifepristone was given orally in a single dose of 600 mg. Each woman was asked to return on day 3, when she received a single oral dose of 400 μg of misoprostol (two 200-μg tablets) and, when necessary, an injection of anti-D(Rho) immunoglobulin. She remained at the center for four hours for measurements of blood pressure and assessment of pelvic pain on a 100-mm visual-analogue scale (from 0 mm, indicating no pain, to 100 mm, indicating severe pain).[22] The women were asked to return 8 to 15 days later for clinical evaluation and measurement of the serum β-hCG concentration, ultrasonography, or both. Hemoglobin concentrations were measured before the administration of mifepristone and at the final visit. Success was defined as the complete expulsion of the conceptus, without the need for an additional surgical procedure. Continuation of pregnancy, incomplete expulsion, and hemorrhage requiring a surgical procedure were considered failures. Tolerance was evaluated, and any prolonged bleeding was assessed during the final visit.

Study 2, from March 1991 through March 1992, involved 390 women at one center. Their mean age was 26±5 years. These women initially received mifepristone and misoprostol as in study 1. If expulsion had not occurred four hours after the administration of misoprostol, the women were offered another 200-μg dose of misoprostol and asked to stay at the center for another two hours. Blood pressure and hemoglobin concentrations were not measured routinely in this study.

Statistical Analysis

Since the study was noncomparative, the statistical analysis was mainly descriptive. The results of study 1 were analyzed with use of Statistical Analysis System (SAS) software (SAS Institute, Cary, N.C.), and those of study 2 with Epistat software (J.L. Gustafson, Round Rock, Tex.). Confidence intervals were determined by solving the quadratic equation.[23] P values (two-tailed) of less than 0.05 were considered to indicate statistical significance.

Results

Study 1

Efficacy was analyzed in 488 women. The mean (±SD) duration of amenorrhea in the 488 women was 45±6 days. When verified by ultrasonography (in 325 women), the duration of pregnancy was estimated to be 42±5 days. Seventeen of the original 505 women were excluded: 1 because of an ectopic pregnancy, 1 who had had amenorrhea for more than 49 days, 1 who was mistakenly given sulprostone instead of misoprostol, and 14 who did not return for follow-up. Among these 14 women, pregnancy was terminated within four hours after the administration of misoprostol in 12, but they were not included in the analysis since the possibility of incomplete expulsion of the conceptus could not be completely excluded.

Among the 488 women, 14 (2.9 percent) did not receive misoprostol because the pregnancy was terminated within the first 48 hours, and 5 (1.0 percent) received a second dose of misoprostol because they vomited soon after receiving the first dose. The overall rate of success was 96.9 percent (95 percent confidence interval, 94.1 to 97.7 percent) (Table 1). Among the women in whom treatment was successful, the mean length of time between the administration of misoprostol and the expulsion of the conceptus was 12±36 hours. The median value was 3 hours, because in the majority of women expulsion took place soon after the administration of misoprostol (60.9 percent in the first 4 hours and 87.2 percent within 24 hours); the longest delay was 12 days.

There were 15 failures (3.1 percent): ongoing pregnancy in 4 women (0.8 percent), incomplete expulsion of the conceptus in 9 (1.8 percent), and hemorrhage requiring hemostatic curettage in 2 (0.4 percent).

All the women had uterine bleeding, whatever the outcome of drug administration. The mean duration of bleeding was 9±4 days (range, 1 to 32); bleeding lasted 12 or fewer days in 85 percent of the women. The mean hemoglobin concentration decreased from 12.8±0.9 g per deciliter (7.9±0.6 mmol per liter) to 12.1±1.0 g per deciliter (7.5±0.6 mmol per liter) at the final visit ($P<0.001$). There was no correlation between this decrease and the duration of the pregnancy as assessed by ultrasonography ($P = 0.10$). The mean decrease in the hemoglobin concentration was similar to that in women who received mifepristone and gemeprost.[9] One woman needed a blood transfusion and hemostatic curettage because the hemoglobin concentration fell from 13.0 g per deciliter (8.1 mmol per liter) to 6.1 g per deciliter (3.8 mmol per liter) nine days after the administration of misoprostol, and another woman underwent curettage for heavy bleeding four hours after the administration of misoprostol.

One woman, in whom an ovarian cyst was diagnosed at the time of entry into the study, had torsion

Table 1. Early Termination of Pregnancy in 488 Women with Mifepristone and a Single Dose of Misoprostol (Study 1).

Outcome Variable	Success*	Failure*	Reason for Failure
	no. (%)		
Administration of mifepristone (600 mg)	—	—	
Abortion without administration of misoprostol	14 (2 9)	—	
Administration of misoprostol followed by abortion within 4 hr	297 (60 9)	1 (0 2)	Heavy bleeding
Later outcome	162 (33 2)	4 (0.8)	Ongoing pregnancy
		9 (1 8)	Partial retention
		1 (0 2)	Prolonged bleeding
Total	473 (96 9)	15 (3 1)	

*Success was defined as termination of the pregnancy and the complete expulsion of the conceptus Failure was defined as indicated Because of rounding, the columns do not add to the percentages shown

of a uterine appendage 10 days after the administration of mifepristone and underwent cystectomy at that time.

Most of the women (80.5 percent) had uterine cramps, for which 16.0 percent received a nonopiate analgesic drug. The pain usually began within one hour after the administration of misoprostol, and it lasted one hour or less. The median intensity of pain recorded (for 484 women) on the visual-analogue scale was 31 mm. During the four-hour monitoring period, nausea, vomiting, and diarrhea occurred in approximately 43 percent, 17 percent, and 14 percent of the women, respectively. The mean systolic and diastolic blood pressure had decreased slightly four hours after the administration of misoprostol. Six women had a substantial but transient decrease in blood pressure (more than 30 mm Hg for the systolic pressure and 15 mm Hg for the diastolic pressure) attributable to a vagal reaction secondary to painful uterine cramps.

Study 2

The mean duration of amenorrhea in the 390 women in study 2 was 45±5 days. Most women had had amenorrhea for less than 50 days, and the duration of amenorrhea was 50 to 59 days in approximately 9 percent. The latter women were included because the date of fertilization was known to be 35 or fewer days earlier. Five women who mistakenly received an additional 400 μg of misoprostol, instead of 200 μg, were not considered further in the analyses reported here (all had complete abortions).

Among the 385 women included in the analysis of efficacy (Table 2), pregnancy was terminated before the administration of misoprostol in 21 (5.5 percent). Pregnancy was terminated within four hours after the administration of 400 μg of misoprostol in 266 women (69.1 percent), and in approximately 90 percent of these women pregnancy was terminated in the first three hours.

Of the 98 women (25.5 percent) who had not aborted after four hours, 71 took an additional 200 μg of misoprostol. Among the 27 women who declined to take the additional dose, 26 aborted completely and 1 had an ongoing pregnancy that was terminated by vacuum aspiration. Of the 71 women who took the additional dose of misoprostol, 40 aborted within 2 hours and 27 within the following 48 hours. Thus, of the 385 women, 305 (79.2 percent) aborted during the monitoring period in the center. Three failures were recorded: one woman who had uterine synechia had an ongoing pregnancy, and two other women had unexplained incomplete abortions. A fourth failure occurred in a woman who should not have been included in the study since she had an ectopic pregnancy and was treated surgically. The overall success rate for this regimen was 98.7 percent (95 percent confidence interval, 96.8 to 99.5 percent).

The mean duration of uterine bleeding was 10±4 days (range, 1 to 30). Bleeding lasted less than 15 days in approximately 90 percent of the women and less than 10 days in approximately 65 percent. No woman in the group received a transfusion. Not taking into account two women who had had amenorrhea for 68 and 80 days, who were enrolled in the study by mistake, and one woman who had minute vaginal spotting for 30 days, there was a positive correlation between the duration of amenorrhea preceding the administration of mifepristone and the duration of bleeding ($r = 0.103$, $P<0.05$). After the exclusion of women whose conceptuses were evacuated instrumentally, the mean duration of bleeding in the women who took 400 μg of misoprostol was 10±4 days, whereas the women who took 600 μg of misoprostol had bleeding for 8±4 days ($P<0.002$). The mean duration of bleeding in the 5 women who took 800 μg of misoprostol was 8±2 days, and it was 10±4 days in the 21 women who had abortions without the administration of prostaglandin.

Uterine cramps were of the same intensity as in study 1, but approximately 50 percent of the women had recurrent cramps after the additional dose of misoprostol. Only 12.5 percent of the women received a nonopiate analgesic drug, and none received an opiate. As in study 1, nausea, vomiting, and diarrhea

Table 2. Early Termination of Pregnancy in 385 Women with Mifepristone and One or Two Doses of Misoprostol (Study 2).

Outcome Variable	Success*	Failure*	Reason for Failure
	no. (%)		
Administration of mifepristone (600 mg)	—	—	
Abortion without administration of misoprostol	21 (5 5)	—	
Administration of the first dose of misoprostol followed by abortion within 4 hr	266 (69 1)	—	
Later outcome			
Second dose of misoprostol declined	26 (6 8)	1 (0 3)	Ongoing pregnancy
Second dose of misoprostol administered	67 (17 4)	2 (0 5)	Partial retention
		1 (0 3)	Synechia with ongoing pregnancy
		1 (0 3)	Ectopic pregnancy
Total	380 (98 7)	5 (1 3)	

*Success was defined as termination of the pregnancy and the complete expulsion of the conceptus Failure was defined as indicated Because of rounding, the columns do not add to the percentages shown

occurred in approximately 40 percent, 15 percent, and 10 percent of the women, respectively. No woman had headache, fatigue, skin rash, or any cardiovascular side effects.

Discussion

The combination of mifepristone and a prostaglandin results in the complete and safe termination of early pregnancy, as demonstrated previously[4,6-9,20] and as confirmed by the results presented here. The oral administration of prostaglandin appears to be an improvement over intramuscular or intravaginal prostaglandin administration for the termination of pregnancy in women who have had amenorrhea for less than 50 days. However, studies of women who have had amenorrhea for longer periods are needed, because mifepristone is approved for use up to day 63 in Great Britain.[6,15] Misoprostol is more convenient than any other prostaglandin, because it is given orally, and compliance is good. The drug is inexpensive, and it can be stored at room temperature.

The misoprostol regimen used in the second study appears to result in success rates that are slightly higher than the rate of approximately 95 percent currently obtained with sulprostone or gemeprost in women who have had amenorrhea for up to 49 days, but this regimen should be studied further before a definitive claim can be made. In our study the administration of the second, smaller dose of misoprostol was often followed by additional uterine cramps, which necessitated the administration of an analgesic drug in approximately 15 percent of the women, but no excessive bleeding or cardiovascular incidents were recorded.

It is not clear whether the second dose of misoprostol significantly shortened the waiting period before abortion, always a difficult time for women to endure. Of the 67 women who took the second dose in study 2 in whom an abortion occurred, over 50 percent of the women aborted within two hours, thus increasing significantly the number of women in whom pregnancy was terminated while they remained in the center. The reported amount of bleeding appeared to be essentially the same as with mifepristone alone,[1,3] with other prostaglandins,[4,6-9,24] or with only one dose of misoprostol.[20,21]

The apparent decrease in the duration of bleeding in the women who received the second dose of misoprostol is encouraging. The correlation between the duration of amenorrhea (and thus the duration of pregnancy) and the duration of bleeding argues for the earliest possible intervention after the decision to have an abortion has been made.

The side effects in the women who received misoprostol were neither more frequent nor more severe than those reported after any other prostaglandin. No woman in either study had a cardiovascular accident. Misoprostol is generally considered to be a safe drug,[25-27] and larger doses (often 800 μg daily) have been given for long periods for other, mostly gastrointestinal indications in patients who are more likely to be smokers or to be at risk for cardiovascular accidents than healthy pregnant women. Until large-scale post-marketing surveillance studies are completed, however, caution should be exercised in using this agent in women at risk for cardiovascular accidents. In any case, the administration of misoprostol alone (not preceded by mifepristone) in order to induce abortion (a practice strongly disapproved of by the distributing company) is particularly unsuitable, since the woman would be exposed to the double risk of insufficient abortive action and embryonic abnormalities.[28-30]

Pregnancies continue in approximately 1 percent of women who receive mifepristone and a prostaglandin.[7-9,15] No teratogenic effects of mifepristone have been reported in nonhuman primates or in humans.[31,32] The malformations reported with the use of misoprostol in illegal or non–medically supervised attempts to induce abortion have occurred after the inappropriate administration of this prostaglandin and always in women who did not receive mifepristone.[28-30] There was only one ongoing pregnancy among the women in study 2, and the regimen may therefore result in fewer ongoing pregnancies than do other regimens of mifepristone plus a prostaglandin.[8,9,33,34] If such a trend is confirmed, the risk of fetal abnormality would be even lower than with other regimens, since in spite of strong advice, some women may not come back for a mechanical abortion if the administration of mifepristone and prostaglandin fails to terminate the pregnancy.

In spite of the satisfactory results reported here, we wish to emphasize that the abortion procedure should continue to be medically supervised.[14] Pregnancy constitutes an empirical risk for women, whether they choose to continue or to terminate it, and medical assistance is a woman's right in either case. In particular, the woman should be examined initially to determine the duration of pregnancy and to exclude ectopic pregnancy and any other medical or surgical contraindication to any method of abortion. Ectopic pregnancy is difficult to detect very early, and its possible occurrence makes a follow-up visit 8 to 15 days after the treatment mandatory, whether pregnancy is terminated by pharmacologic or surgical methods. It is too early to determine whether it will become possible to use the mifepristone–misoprostol method, under medical control, outside specialized centers.

In conclusion, we found in the studies reported here that, for the termination of pregnancy in women who had had amenorrhea for less than 50 days, orally administered misoprostol, in conjunction with mifepristone, is at least as successful and as well tolerated as other prostaglandins given parenterally or vaginally. This new regimen is simpler and potentially allows greater privacy than any other abortion method, and it has recently been approved in France. We suggest that mifepristone followed 48 hours later by misoprostol is a convenient and safe regimen for the early termination of pregnancy, but the possibil-

ity of rare accidents cannot be excluded, and caution should be exercised.

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ANDERSON ADVISORY, INC.

May 6, 1994

Representative Pat Schroeder
United States Congress
Rayburn House Office Building
Washington, D.C. 20515

Dear Pat:

David and I wanted you to know that RU-486 has erased any sign of the four brain tumors David had when we met you in July, 1992.

David had an MRI yesterday after which we met with the doctor and received this wonderful news. The side-effects are minimal (certainly less than those of his three surgeries). Our family is living a normal, productive (and grateful) life.

We continue to thank you, Representative Wyden and your staffs for making this life-saving medicine available.

Sincerely,

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